

Patterns of exogenous insulin requirement reflect insulin sensitivity changes in trauma

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Abstract

Introduction: We investigated patterns of blood glucose and exogenous insulin requirement in the intensive care unit, and questioned whether they reflect fluctuations in insulin activity.

Methods: Records for burn intensive care unit patients with 7 days of glucose control with insulin were reviewed. Hourly blood glucose and insulin dose were matched for time collected and analyzed with linear and cosine regression. Frequency analysis identified recurring patterns.

Results: Diurnal patterns of blood glucose and insulin requirement were noted (insulin troughs = noon; insulin peaks = midnight; glucose troughs = 5 AM; glucose peaks = 5 PM). Average insulin requirement increased at a constant linear rate (slope = .013, $r^2 = .57$, $P \leq .001$).

Conclusions: Diurnal patterns in blood glucose and insulin requirement mirror those of healthy subjects and may reflect persistence of normal variability in insulin activity. The 5-hour offset in peaks and troughs is suggestive of complex interplay between insulin availability and receptor sensitivity. The insulin requirement to blood glucose ratio increased, evidence that insulin resistance progresses over time. © 2007 Excerpta Medica Inc. All rights reserved.

Keywords: Hyperglycemia; Trauma; Diurnal variation; Circadian rhythm; Insulin sensitivity; Insulin resistance

Multiple studies have demonstrated the association in critical injury of hyperglycemia with increased morbidity and mortality [1–8], and this has led in turn to widespread adoption of intensive insulin protocols aimed at maintaining blood glucose within tight parameters [9–12]. However, such protocols are difficult to implement because glucose and insulin patterns in trauma are poorly understood. Recent work in mixed intensive care units (ICUs) found that glucose variability is also associated with poor outcomes [13–15], thus merely controlling hyperglycemia may not be sufficient. A clear understanding of normal and abnormal variance in glucose and insulin in critical injury may be necessary to adequately maintain glucose homeostasis.

Glucose regulation in healthy subjects is characterized by maintenance of blood glucose within narrow parameters [16]; however, within this tight range, glucose fluctuates in a diurnal pattern [17]. The circadian rhythm is characterized by a nadir in the morning, followed by a peak in the evening [17]. Other molecules involved in glycemic regulation display similar circadian rhythms, including insulin, cortisol, and leptin [17–20]. Plasma insulin clearance is typically lower at night, and higher during the day, reflecting changes in insulin receptor sensitivity [19]. During the day, when a majority of calories are ingested, insulin activity is at its highest, subsequently declining at night [17–20]. This is manifested in diabetics as the “dawn phenomenon,” a term used to describe the observed increase in insulin requirement at night in these patients [17].

In acute injury, diurnal variance of cortisol and leptin are known to be blunted or absent [21], and as a result, similar attenuation of glucose and insulin diurnal patterns might be

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Table 1
Population demographics

Variable	Value	Number of subjects
TBSA burned (%)	35 ± 23	129
ISS	18 ± 11	92
Inhalation injury (%)	26	153
Polytrauma (%)	9	147
Average corrected glucose (mg/dL)	120 ± 24	156
Age (y)	46 ± 20	156
Percent female	24	156

TBSA = total body surface area; ISS = Injury Severity Score.

assumed to be present. However current research in mixed ICUs changed this view, as preservation of glucose circadian rhythms was demonstrated [22]. Circadian rhythms of glucose metabolism in trauma patients remain to be characterized, and insulin patterns have not been examined in any ICU population.

Glycemic dysregulation in critical injury is common, and manifests as acute and long-term hyperglycemia. Insulin resistance is thought to play a role, perpetuating hyperglycemia and, in consequence, exacerbating catabolism [23–25]. We investigated whether variability in blood glucose levels and exogenous insulin requirement reflect fluctuations in underlying insulin sensitivity. We wondered whether: (1) glucose diurnal patterns are preserved in trauma patients; (2) insulin diurnal patterns are preserved in trauma patients; and (3) increased insulin resistance is demonstrated by comparison of glucose and insulin patterns.

Methods

After regulatory approval was obtained, records were reviewed for all patients admitted to a single burn ICU, and data were collected from January 1, 2002 to December 31, 2004 for those who received a minimum of 7 days of insulin treatment to maintain glucose control. The insulin nomogram was determined by physician preference until August 2003, when a standardized protocol was adopted (Appendix A). Demographic information included total body surface area burned, injury severity score, polytrauma, age, gender, and presence of inhalation injury. Initial and average glucose was calculated for the population. Outcome variables were collected, including incidence of mortality, pneumonia, bacteremia, sepsis, and acute respiratory distress syndrome (ARDS), and these data were combined to determine the percent of subjects with single and multiple complications. Pneumonia was defined as a new, persistent radiographic infiltrate with 2 of the 3 following clinical criteria: fever $\geq 38^\circ\text{C}$, leukocytosis $\geq 12 \times 10^9/\text{L}$ or leukopenia $\leq 4 \times 10^9/\text{L}$, and purulent respiratory secretions [26]. Sepsis was defined as a known or suspected infection in the presence of 2 or more of the following criteria: (1) core temperature $\geq 38^\circ\text{C}$ (100.4°F) or $\leq 36^\circ\text{C}$ (96.8°F); (2) heart rate ≥ 90 beats/min; (3) respiratory rate ≥ 20 breaths/min or PaCO_2 of ≥ 32 mm Hg; and (4) white blood cell count of $\geq 12,000/\mu\text{L}$ or $\leq 4,000/\mu\text{L}$ or $\geq 10\%$ immature neutrophils [27]. ARDS was diagnosed for P/F ratio ≤ 200 , bilateral pulmonary infiltrates on chest radiograph, in the absence of clinical evidence of left atrial hypertension (or a pulmonary-capillary wedge pressure of > 18 mm Hg, if measured) [28].

Point-of-care glucometer readings were collected and a correction formula applied to adjust for hematocrit effect in this profoundly anemic population [29]. Hourly blood glucose and insulin dose requirement were matched between subjects for time of day given, and the glucose values averaged to obtain a 24-hour curve. Average blood glucose and insulin requirement for the study population were plotted with application of linear and cosine regression to determine daily and overall trends. Data filtration and frequency analysis identified periodicity of recurring patterns. Comparison was then made between blood glucose and exogenous insulin levels in the population.

Initial and average blood glucose means \pm SD were calculated. Periodicity was determined with frequency analysis. Diurnal glycemic and insulin requirement variability was analyzed by simple regression and cosine regression, and significance evaluated with Student *t* test. Quantitative variables with normal distribution were analyzed using Student *t* test; when distribution was not normal, the nonparametric Mann-Whitney test was used. Simple chi-square tests were used for qualitative variables. Tests were 2-sided in all cases. Significance level was set at .05.

Results

Review of admissions to our burn unit over 54 months identified 156 eligible subjects. Total body surface area burned was $35\% \pm 23\%$, Injury Severity Score was 18 ± 11 , and age was 46 ± 20 years (Table 1). Among outcome measures evaluated were mortality, incidence of pneumonia, ARDS, bacteremia, and sepsis, and these were combined to provide the percent of subjects that experienced single and multiple complications (Table 2). Average initial glucose was 148 ± 61 mg/dL, and trended down sharply over the first 24 hours to a mean of 120 ± 24 with insulin treatment. On days 2 through 7, blood glucose levels and exogenous insulin requirement each exhibited an underlying cyclic pattern (Fig. 1). Frequency analysis demonstrated that both were diurnal in nature (Fig. 2), with peaks at 24 hours. However, cosine regression of the insulin requirement and blood glucose data demonstrated that the respective troughs and peaks were offset by 5 hours. Those for blood glucose were at 5 AM and 5 PM, while troughs and peaks for exogenous insulin dose were at noon and midnight, respectively (Fig. 3). Cosine regression confirmed the diurnal glucose and insulin patterns for both; a paired *t* test between the glucose cosine wave and our blood glucose data renders an r^2 of .65 ($P \leq .001$), while the correlation for the insulin requirement cosine wave and our data was $r^2 = .64$ ($P \leq .001$).

Table 2
Outcome measures

Measure	%	n
Mortality	21	156
Pneumonia	30	134
Bacteremia	13	120
Sepsis	11	127
ARDS	9	136
Complications	56	156
Multiple complications	22	156

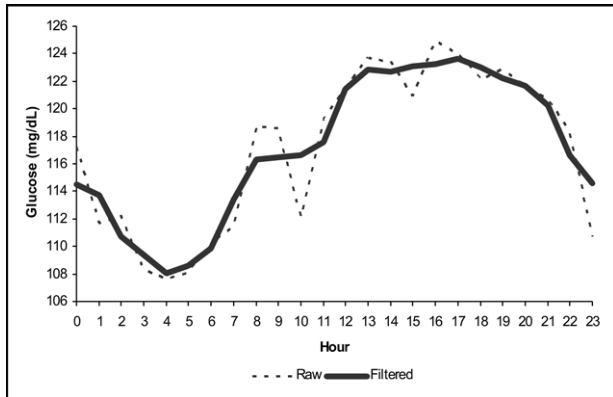


Fig. 1. Diurnal pattern of raw versus filtered blood glucose over 24 hours for the population studied, demonstrating an early morning trough and evening peak.

While cosine regression clarifies the pattern of glucose and insulin regulation, simple regression of the data identifies the overall trend in mean levels. The average insulin dose to correct hyperglycemia in the study population was lowest at admission and increased at a constant rate (slope = .013, $r^2 = .57$, $P \leq .001$) during the first 7 days of admission. In contrast, after the initial decline in blood glucose, a simple regression line expressing the average glucose is nearly a horizontal line (slope = .001, Fig. 3). The combination of a constantly increasing average daily insulin requirement, with little to no change in mean glucose levels, is evidence that insulin activity decreases over the ICU course. Conversely, preservation of normal glucose and

insulin diurnal variation suggests that circadian changes in insulin receptor sensitivity may persist.

Comments

Hyperglycemia has become a major target of therapy in most ICUs after intensive insulin therapy was shown to improve morbidity and mortality [9–12]. However, efforts to maintain glucose within tight physiologic parameters are hampered by a paucity of knowledge regarding the impact of critical injury on normal glucose and insulin curves. Normal subjects display diurnal variation in several molecules involved in glucose metabolism, including glucose itself, insulin, cortisol, and leptin [17–20]. Glycemic regulation in trauma is disordered, evidenced by hyperglycemia, which is common [1–7]. Historically, this was considered a beneficial response related to the “fight or flight” stress reaction; this view has since been replaced by the recognition that outcomes are improved with tight glucose control, usually with exogenous insulin. In a similar fashion, diurnal glucose and insulin variability was assumed to be attenuated or absent, after demonstration of these changes in cortisol and leptin circadian rhythms [21].

Our data show that blood glucose diurnal patterns are preserved after injury, findings that are similar to those previously reported in a mixed ICU population [22]. Mean glucose, however, remains stable or decreases after an initial precipitous decline in the first 24 hours. It would be tempting to conclude that insulin activity is not reduced, but comparison of the glucose simple regression line to that of insulin requirement dispels this notion. Increasingly higher levels of insulin are required to maintain a constant blood

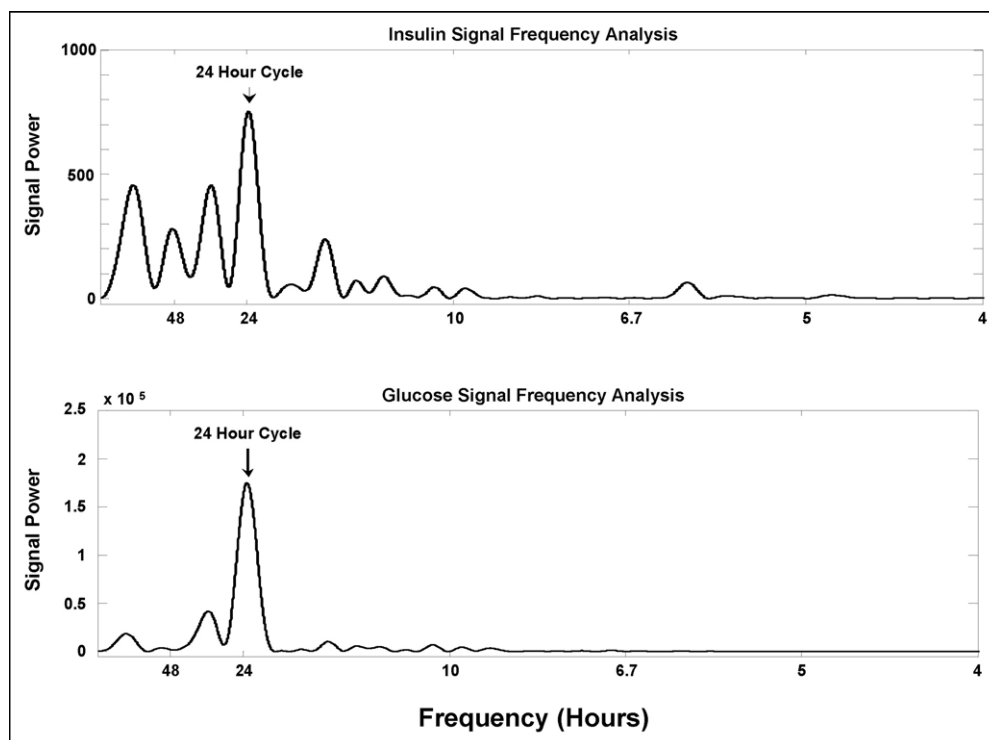


Fig. 2. Diurnal pattern of blood glucose confirmed by frequency analysis demonstrating a strong peak at 24 hours. A similar peak at 24 hours identified the diurnal pattern of insulin requirement.

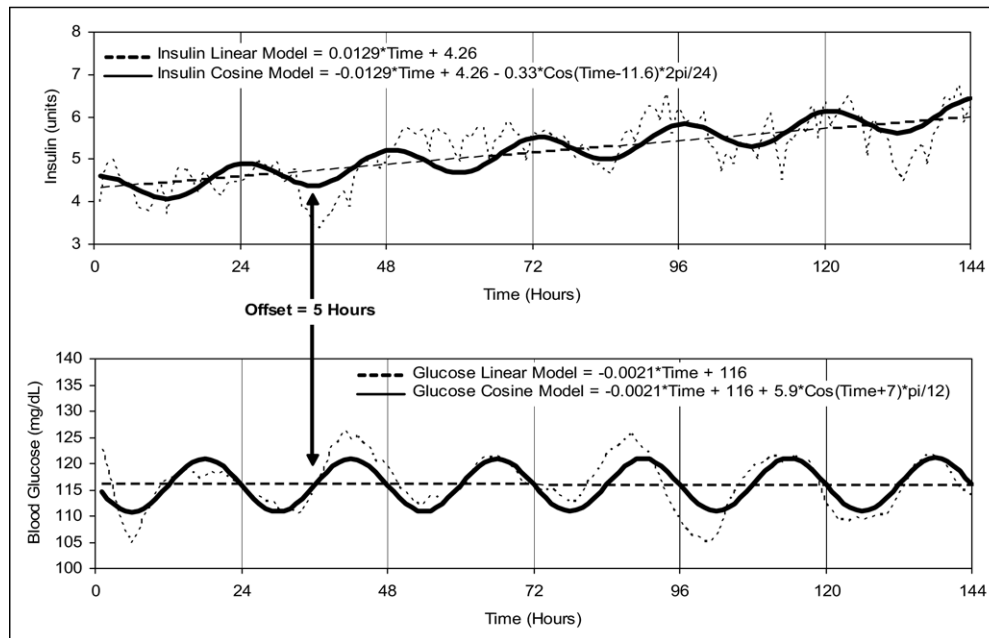


Fig. 3. Diurnal patterns over time of insulin requirement (top) and blood glucose (bottom). Simple regression formula for insulin requirement (large dash) demonstrates that the slope increases over time, while that of glucose remains nearly constant. Diurnal peaks and troughs are offset by 5 hours.

glucose level over time, evidence of diminishing insulin activity and/or growing insulin resistance after injury. Clinical conditions other than severe burns and trauma are also known causes of increased insulin requirement, including, but not limited to, sepsis, steroid use, and frequent trips to the operating room. Causative relationships are beyond the scope of this study but merit further investigation to elucidate underlying mechanisms and identify potential targets of therapy.

Diurnal variation in insulin requirements continues to be seen and may reflect persistence of normal changes in insulin receptor sensitivity; in normal subjects, receptors are relatively resistant at night. This is perhaps a conserved protective mechanism to prevent hypoglycemia during fasting hours. Peaks and troughs for exogenous insulin requirement follow those for blood glucose by 5 hours. The half-life of intravenous regular insulin is 7 minutes; thus the offset likely reflects complex interactions between glucose production and insulin receptor activity. This is further supported by the fact that the nocturnal exogenous insulin peak reflects a similar nighttime insulin insensitivity in the healthy subjects. This finding has clinical implications for how patients are fed. Currently, continuous feeding strategies predominate; however, if insulin receptor sensitivity continues to wax and wane in the critically injured, such a schedule may hamper attempts at insulin control, by providing calories when the body is less able to metabolize them. A return to bolus feeding during daylight hours may be beneficial and allow for better glucose control. Further studies are needed to define and test this notion.

Normal diurnal variation in glucose metabolism persists after injury; however abnormal variability also is present. Studies conducted in mixed ICU settings demonstrated that increased variability is associated with higher mortality, and our center found that this association is also present after

injury [13–15]. Inappropriate application of intensive insulin therapies during decreased insulin receptor activity combined with feeding during times of relative insulin resistance may drive blood glucose outside the target range, triggering counter-regulatory mechanisms, and thus increasing overall variability. This may, in turn, result in worsened outcomes. Further research is needed to fully characterize changes in insulin receptor sensitivity, and use the knowledge gained to refine both insulin and nutritional strategies.

This study has several limitations; it is a retrospective review, and cannot show causality. The interplay between blood glucose and insulin requirement in this population has enhanced our understanding of glucose metabolism in the critically injured; however, the analysis would be enriched by the addition of nutritional intake, total blood insulin concentration, C-peptide (a measure of endogenous insulin), and cortisol levels. Ideally, this information could be coupled with isotope studies providing data regarding hepatic glucose production, rate of glucose metabolism, and insulin receptor function. Despite these limitations, this study provides evidence that glucose metabolism in the critically injured is characterized by a high degree of complexity, and may be responsible for difficulties encountered in maintaining physiologic euglycemia.

Conclusions

Diurnal patterns of insulin requirement in critical injury mirror insulin levels in healthy subjects, and may reflect persistence of normal variability in insulin sensitivity. Insulin requirement peaks and troughs (midnight and noon, respectively) are likely inversely related to normal fluctuations in insulin sensitivity, which peaks during daylight hours, when calorie consumption is high. Conversely, fasting at night is physiologically normal and corresponds to

decreased insulin sensitivity. The zenith and nadir of glucose levels follow that of insulin; the 5-hour time lag is suggestive of the complex interplay between insulin availability and receptor sensitivity. The normal sinusoidal pattern of insulin and glucose regulation appears to be preserved in the critically injured, and indicate that the use of continuous feeding strategies in this population may need to be revisited. Further research is needed to investigate whether a continuous nutritional schedule is optimal, or whether a return to bolus feeding would be beneficial. Insulin resistance progressively increases in early trauma, and knowledge of normal and abnormal patterns may improve efforts at maintaining euglycemia.

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Appendix A

Insulin Protocol Effective From August 15, 2003 to October 1, 2003

Treatment with intravenously administered human regular insulin (1 U/mL, Novo Nordisk, Princeton, NJ) was initiated when blood glucose surpassed 150 mg/dL, at the dose of 2 U/h for glucose 201–300 mg/dL, with 1-U/h increases until glucose was between 151 and 200 mg/dL. The intravenous insulin infusion was titrated according to the following parameters: insulin was held and 50 mL of 50% percent dextrose (Hospira, Inc, Lake Forest, IL) given for glucose less than 60 mg/dL; glucose between 60 and 100 mg/dL resulted in holding of the infusion for one hour; when glucose was between 101 and 100 mg/dL, the infusion was decreased by one units; glucose levels between 151 and 200 prompted no change. Glucose levels from 201 to 300 mg/dL and 301 to 400 mg/dL triggered a rate increase of 1 U, and a bolus of 2 and 4 U, respectively. Physician assistance was sought for glucose greater than 400 or less than 60 mg/dL.

Insulin Protocol Effective From October 1, 2003 to Present

Treatment with intravenously administered human regular insulin (1 U/mL, Novo Nordisk) was initiated when

blood glucose surpassed 120 mg/dL, at the dose of 1 U/h for glucose 120–150 mg/dL, 2 U/h if glucose was between 151 and 200 mg/dL, and 4 U/h if initial glucose surpassed 200 mg/dL. The intravenous insulin infusion was titrated according to the following parameters: insulin was held and 25 mL of 50% dextrose (Hospira, Inc) given for glucose less than 60 mg/dL; glucose between 60 and 79 mg/dL resulted in holding of the infusion until glucose normalized and restarting at 50% of the previous rate; when glucose was between 80 and 110 mg/dL, the infusion was adjusted by 0 to .5 U in response to increasing and decreasing trends; glucose levels between 111–150, 151–200, and 201–250 mg/dL triggered rate increases of .5, 1, and 2 U, respectively. Physician assistance was sought for glucose greater than 250 or less than 60 mg/dL [9].

Discussion

Richard Barton, M.D. (Salt Lake City, UT): The authors report a retrospective study in which they recorded hourly blood glucose measurements and exogenously administered insulin in 156 burn patients. They demonstrated 3 significant findings. First, the glucose reached a nadir at approximately 5:00 in the morning and peaked at approximately 5:00 in the evening, and that this diurnal pattern persisted over the 7-day study period. Second, they demonstrated that exogenously administered insulin dose followed a similar diurnal pattern, but with the 5-hour offset that they described, and, finally, they showed that despite diurnal variations in glucose and insulin requirements, that insulin requirements tended to increase steadily over the 7-day period in order to maintain target levels of glucose. The authors note that the diurnal variation in glucose seen in burn patients parallels that seen in normal subjects. They suggest that the steady increase in insulin requirement over the 7-day period reflects decreasing insulin activity and/or growing insulin resistance. I think there are alternative explanations for this increasing insulin requirement. In the stressed patient, glucose is produced via hepatic gluconeogenesis and glycogenolysis, under the influence of catecholamines, cortisol, and glucagon. Van den Berghe [1] recently demonstrated decreasing insulin requirements over time in a population of critically ill surgical patients. In this population of burned patients, increased levels of metabolic stress, caused by infection and perhaps repeated operative procedures, might have been responsible for the increased glucose production and insulin requirements. Further, it is important to remember that glucose transport occurs down its concentration gradient, is facilitated by carrier proteins, and occurs via insulin-mediated as well as non-insulin-mediated pathways. In critically ill patients, insulin-mediated

hepatic glucose uptake is known to be decreased, while non-insulin-mediated glucose uptake in other tissues, such as the central nervous system, is increased. Hepatic insulin resistance has been shown to be associated with increased circulating levels of insulin-like growth factor (IGF)-binding protein-1, but of course IGF-binding protein-1 was not measured in this study.

Regardless of the mechanisms involved, this study demonstrates that glucose levels vary diurnally in burn patients, and that insulin requirements increased over time.

I have 3 questions:

1. Were these patients subjected to burn wound excision and grafting during the 7-day study period that, due to increased levels of metabolic stress, might have explained the increased insulin requirement?
2. Further, in a related question, did glucose intake, due to the initiation of, or increase in, nutrition support increase over the 7-day study period?
3. Based on the diurnal variation that you demonstrated in glucose levels and insulin requirements, and assuming that this variation in glucose level might be clinically significant in terms of infectious complications, how would you recommend that we alter the administration of nutrition support to minimize this variation?

Heather Pidcoke, M.D. (Fort Sam Houston, TX): To answer the first question, the subjects did undergo excision and grafting. This may have contributed to increased stress; however, burn patients who are severely injured are maximally stressed. In answer to your question regarding nutrition, we typically start patients on nutrition as early as possible and in the first 7 days, it is possible that it may have taken the entire 7 days to get them up to go, however, we get them up to go sooner than that. Your final question was regarding what we should do in response to the study. Because it is a retrospective review, I think more studies are needed before we change treatment; however, it certainly poses the question as to whether continuous feeding is the right way—what right way to feed the patients and perhaps a 12-hour at the daytime feeding and 12-hour at night feeding might be something to study in order to see if patients do better because there have been studies documenting that in healthy patients at least, the insulin receptor is more sensitive during daylight hours. Again, I am not recommending this in response to this study. It is a retrospective review and the question needs further study.

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